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Women and Heart Disease: An Evidence-Based Update

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ABSTRACT

One in 4 American women die of cardiovascular disease despite strong campaigns to reduce the incidence of this condition. Unfortunately, the first symptom for half of all women with ischemic heart disease remains sudden cardiac death, which means providers are overlooking the presence of this disease in females until it is too late. Not only do women often present differently than men, women have underlying gender differences in the pathophysiology of ischemic disease. In this review we present a summary of current evidence on how to identify, diagnosis, and appropriately treat ischemic heart disease, including microvascular dysfunction, in females.

Keywords: atherosclerosis, cardiac syndrome X, ischemic heart disease, microvascular dysfunction, women

INTRODUCTION

Although statistics released by the United States Centers for Disease Control and Prevention (CDC) reveal that death rates from ischemic heart disease (IHD) have fallen by almost 30% since 1999, 1 in every 4 American women still die as a direct result of heart disease.[1] Despite intense educational campaigns by organizations such as the American Heart Association, almost half of American women remain unaware that heart disease is the leading cause of mortality among females in the US. Even fewer women are aware of the heart disease process called microvascular dysfunction that impairs coronary perfusion and can cause sudden cardiac death.[1] The purpose of this literature review is to discuss IHD in women and to review recent evidence on the subject. This includes: (a) a review of the underlying pathophysiology of heart disease in females, including microvascular dysfunction; (b) an analysis of the unique presentation of heart disease in women; (c) an exploration of the challenges of diagnosing IHD in women; (d) a discussion of preventive strategies; and (e) a review of current treatment options for females with IHD.

PATHOPHYSIOLOGY OF IHD

The pathophysiology of heart disease has gender differences that are poorly understood due to a lack of research in this area. Generally, chronic inflammation leads to the process of atherosclerosis where plaque begins to accumulate on arterial vessel walls. The atherosclerotic build-up eventually results in narrowing of the vessels and this can lead to plaque rupture causing an acute coronary event. In females, the plaque is more likely to lead to positive vessel remodeling with diffuse, nonobstructive disease (usually defined as $< 70\%$ stenosis of any coronary vessel measuring > 2 mm in diameter).[2] Unfortunately, this type of plaque tends to be more unstable than the plaque developed in negative remodeling that is more prominently seen in males. These lipid-rich vulnerable plaques incline women to more lethal cardiac outcomes and, after menopause, these plaques are more likely to calcify.[3,4] After 75 years of age, women are actually more likely than men to have an acute coronary event.[5] Women also have smaller coronary arteries as well as less collateral circulation than men.[6]

In women without significant coronary artery disease that limits blood flow there can be other underlying

causes of ischemia, such as microvascular dysfunction, endothelial dysfunction, and coronary artery spasm. This combination is often called cardiac syndrome X (CSX), previously believed to be a benign condition.[7] Microvascular dysfunction causes alteration in normal coronary blood flow. The arteries involved in these complications are tiny (many are smaller than a human hair) and, when affected, the vessels malfunction. The malfunctioning leads to arteries that fail to appropriately dilate, that overconstrict, or that respond with a combination of both. The response can cause an impaired myocardial blood supply and, subsequently, ischemia.[8] The pathogenesis of microvascular dysfunction is not fully understood and research is ongoing.[7] Endothelial dysfunction results from damage to the vasculature caused by oxidative stress. Endothelial dysfunction may directly promote development of atherosclerosis as well as vasospasm. In turn, vasospasm is thought to result in plaque erosion. These eroded sites can contribute to thrombus formation and an acute coronary event. In women, plaque erosion is more common than plaque rupture, but, in patients with CSX, plaque rupture is still the cause of death in one third of all female cardiac events, as compared with less than one sixth of all male cardiac events.[3,9] Consequently, rupture and erosion of plaque both commonly cause significant negative cardiac outcomes in women.[8] Coronary vasospasm has many possible causes and is thought to be partially attributable to genetics.[8] Myocardial bridging (when a coronary artery tunnels beneath the myocardium instead of laying on top of the muscle) may also cause symptoms.[10]

Both men and women can develop microvascular dysfunction, especially at an older age and in the presence of multiple risk factors.[11] However, women appear to be more vulnerable to the effects of diabetes, insulin resistance, and hormones on their vessels. Estrogen, in particular, enhances endothelial function and reduces pain perception. Estrogen also has a positive effect on serum lipids and, conversely, an estrogen deficiency can lead to insulin resistance. Estrogen levels naturally fall as women age beginning in perimenopause, but emotional or physical stress may also cause estrogen levels to drop.[12] Other risk factors for the development of microvascular dysfunction include smoking, hyperlipidemia, hypertension, diabetes mellitus, and inflammation associated with autoimmune processes such as systemic lupus erythematosus.[10]

Diet may also play a role in IHD. One study revealed a link between high-fat and high-protein diets and the development of abnormal coronary perfusion patterns.[13] Another small study suggested that low vitamin D levels may lead to ischemic symptoms.[14] Intake of soy-based phytoestrogens by women may be linked to increased coronary microvascular dysfunction.[15]

Women are also more likely than men to have other forms of non-atherosclerotic coronary heart disease, which includes spontaneous coronary artery dissection, coronary fibromuscular dysplasia, vasculitis, coronary embolism, and congenital abnormalities of the coronary arteries.[12,16] Spontaneous coronary artery dissection (even in the absence of coronary atherosclerosis) occurs more commonly in women than men, with 80% of all cases occurring in women. Dissection leads to increased mortality rates and may be the cause of up to 25% of all myocardial infarctions in women $<$ 55 years of age.[3,11,16]

It is important to understand that, because of all of these underlying issues, women who present with angina symptoms may very well be at risk of an acute coronary event, even if angiography reveals nonobstructive coronary artery disease or normal-appearing coronary vessels. Indeed, almost 75% of women with typical angina symptoms have no angiographic limitation of blood flow and, unfortunately, "open coronaries" on angiography does not necessarily convey a positive prognosis.[7,8] Symptomatic women with nonobstructive disease on angiography appear to have an increased risk of myocardial events and cardiac mortality than asymptomatic females.[17] In addition to these adverse outcomes, many female patients become disabled by constant cardiac symptoms, resulting in a decreased quality of life.[8] The number of persistently symptomatic women with nonobstructive IHD has also gravely affected overall health care costs, with each woman's lifetime treatment expenses exceeding US$750,000.[18]

PRESENTATION OF IHD IN WOMEN

Women present with IHD approximately 1 decade later in life than their male counterparts. This later onset has created a misconception that females are not